REMARKS

The Office Action and Applicant's Response to Restriction Requirement

The Examiner required restriction, under 35 U.S.C. § 121, and required Applicant to elect a single invention to which the claims must be restricted. The Examiner designated three claim groups.

In response, Applicant elects designated claim **Group II** (directed to an in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a **neuronal cell**; to a transdifferentiated cell of epidermal origin having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell produced by the method; to a cell culture derived from the transdifferentiated cell; to a transdifferentiated cell of epidermal origin and cultured in vitro; and to a kit for transdifferentiating, in vitro, an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell).

Applicant has herein canceled Claims 25, 26, 37, and 38, as being directed to a non-elected group and has amended Claims 1, 17, 28, 29, 39, 43, and 49, in accordance with Applicant's election, to remove the recitation of "neural progenitor cells", "glial cells", and signal molecules and markers inapplicable to neuronal cells, as being directed to non-elected subject matter. Although canceled Claims 13, 20, 24, 31, and 32 were directed to elected subject matter, Applicant considers them to be redundant in view of the limitations of thrice amended Claim 1, step (d).

Amendments to Claims 22 and 23, changing dependency to being from Claim 17 instead of from Claim 20, are made for the sake of greater clarity in view of the cancellation herein of Claim 20.

Amendments to Claims 33 and 34, changing dependency to being from Claim 29 instead of from Claim 31, are made for the sake of greater clarity in view of the cancellation herein of Claim 31.

Applicant's election is made with a complete reservation of all rights under 35 U.S.C. § 121.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

Please cancel Claims 13, 20, 24-26, 31, 32, 37, and 38, without prejudice, as being directed to a non-elected claim group. Please amend Claims 1, 17, 22, 23, 28, 29, 33, 34, 39, 43, and 49 as follows.

1. (Thrice Amended) An in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a [neural progenitor,]neuronal[, or glial] cell, comprising:

(a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

(b) exposing the cell(s) to an amount of an antagonist of bone morphogenetic protein (BMP) effective to antagonize endogenous BMP signal transduction activity;

(c) growing the cell(s) in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or a segment of a human HES1 gene, or homologous non-human counterpart of either of these, in an amount effective to suppress the expression of functional gene product of MSX1 and/or HES1, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a [neural progenitor,]neuronal[, or glial] cell; and

(d) growing the transdifferentiated cell in a medium comprising a retinoid compound and a signal molecule selected from the group consisting of [brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), neurotrophin (NT)-3, neurotrophin (NT)-4, IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide, wherein:

(i) said signal molecule, being selected from the group consisting of sonic hedgehog and sonic hedgehog aminoterminal peptide, the physiological and/or immunological feature

comprises expression of a neural progenitor cell marker selected from the group consisting of nestin and neural RNA-binding protein Musashi, or a combination of these;

(ii) said signal molecule, being selected from the group consisting of] brain-derived neurotrophic factor (BDNF), platelet derived growth factor (PDGF), nerve growth factor (NGF), sonic hedgehog, sonic hedgehog aminoterminal peptide, neurotrophin (NT)-3, and neurotrophin (NT)-4[,]; and

wherein the physiological and/or immunological feature comprises expression of a neuronal cell marker selected from the group consisting of neurofilament M, neural-specific β-tubulin, neural-specific enolase, and microtubule associated protein 2, or a combination of any of these; and wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length[; and

(iii) said signal molecule, being selected from the group consisting of ciliary neurotrophic factor (CNTF), IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide, the physiological and/or immunological feature comprises expression of a glial cell marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4].

2. (Reiterated) The method of Claim 1, wherein the subject is a human.

3. (Reiterated) The method of Claim 1, wherein the epidermal basal cell(s) is derived from a skin biopsy.

4. (Reiterated) The method of Claim 1, wherein culturing the proliferating epidermal basal cell population further comprises separating keratinized epidermal cells from the epidermal basal cells in a calcium-free medium.

5. (Reiterated) The method of Claim 1, wherein the amount of the antagonist of bone morphogenetic protein is about 10^{-6} to 10^{-4} M.

6. (Reiterated) The method of Claim 5, wherein the amount of the antagonist of bone morphogenetic protein is about 5×10^{-6} to 5×10^{-5} M.

7. (Reiterated) The method of Claim 1, wherein the antagonist of bone morphogenetic protein (BMP) is fetuin, noggin, chordin, gremlin, or follistatin.

8. (Reiterated) The method of Claim 7, wherein the fetuin is mammalian or avian fetuin.

9. (Reiterated) The method of Claim 8, wherein the mammalian fetuin is human, bovine, porcine, ovine, or equine fetuin.

10. (Reiterated) The method of Claim 1, wherein the antisense oligonucleotide(s) is modified with one or more thio groups.

11. (Reiterated) The method of Claim 1, wherein the amount of the antisense oligonucleotide is about 5×10^{-6} M to about 10^{-5} M.

13. (Canceled)

15. (Reiterated) The method of Claim 1, wherein the retinoid compound is all-trans retinoic acid or Vitamin A.

17. (Amended) A transdifferentiated cell of epidermal origin having one or more morphological, physiological and/or immunological feature(s) of a [neural progenitor,]neuronal[, or glial] cell produced by the method of Claim 1.

19. (Reiterated) The transdifferentiated cell of Claim 17, wherein the cell further exhibits a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

20. (Canceled)

22. (Amended) The transdifferentiated cell of Claim [20]17, wherein the cell is a GABAergic cell.

23. (Amended) The transdifferentiated cell of Claim [20]17, wherein the cell is a dopaminergic cell.

24. (Canceled)

25. (Canceled)

26. (Canceled)

27. (Reiterated) The transdifferentiated cell of Claim 17, wherein the cell is of human origin.

28. (Amended) A cell culture derived from the transdifferentiated cell of Claim 17, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a [neural progenitor,]neuronal[, or glial] cell.

29. (Twice Amended) A transdifferentiated cell of epidermal origin and cultured in vitro, comprising a cell of epidermal basal cell origin, said transdifferentiated cell displaying one or more morphological, physiological and/or immunological feature(s) of a [neural progenitor,]neuronal[, or glial] cell, wherein the physiological and/or immunological feature comprises expression of a marker selected from the group consisting of [nestin, neural RNA-binding protein Musashi,]neurofilament M, neural-specific β-tubulin, neural-specific enolase, and microtubule associated protein 2[, glial fibrillary acidic protein (GFAP), O4], or a combination of any of these.

30. (Reiterated) The transdifferentiated cell of Claim 29, wherein the cell further displays the physiological feature of a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

31. (Canceled)

32. (Canceled)

33. (Amended) The transdifferentiated cell of Claim [31]29, wherein the cell is a GABAergic cell.

34. (Amended) The transdifferentiated cell of Claim [31]29, wherein the cell is a dopaminergic cell.

35. (Reiterated) The transdifferentiated cell of Claim 29, wherein the morphological feature comprises one or more neurite-like process(es) at least about 50 micrometers in length.

36. (Reiterated) The transdifferentiated cell of Claim 29, wherein the cell is of human origin.

37. (Canceled)

38. (Canceled)

39. (Amended) A cell culture derived from the transdifferentiated cell of Claim 29, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a [neural progenitor,]neuronal[, or glial] cell.

43. (Twice Amended) A kit for transdifferentiating, in vitro, an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a [neural

progenitor,]neuronal[, or glial] cell, comprising:

(A) an antagonist of bone morphogenetic protein (BMP);

(B) at least one antisense oligonucleotide comprising a segment of a human MSX1 gene, a segment of a human HES1 gene, or a non-human homologous counterpart of either of these; and

(C) a retinoid compound and a signal molecule selected from the group consisting of brain-derived neurotrophic factor (BDNF), [ciliary neurotrophic factor (CNTF),] platelet-derived growth factor (PDGF), nerve growth factor (NGF), neurotrophin (NT)-3, neurotrophin (NT)-4[, IL-6], sonic hedgehog, and sonic hedgehog aminoterminal peptide.

44. (Reiterated) The kit of Claim 43, further comprising instructions for using (A), (B), and (C) in transdifferentiating a subject's epidermal basal cell(s).

45. (Reiterated) The kit of Claim 43, wherein the antagonist of bone morphogenetic protein (BMP) is fetuin, noggin, chordin, gremlin, or follistatin.

47. (Reiterated) The kit of Claim 43, wherein the retinoid compound is all-trans retinoic acid or Vitamin A.

49. (Reiterated) An in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell, comprising:

(a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

(b) exposing the cell(s) to an amount of an antagonist of bone morphogenetic protein (BMP) effective to antagonize endogenous BMP signal transduction activity;

(c) growing the cell(s) in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or a segment of a human HES1 gene, or homologous non-human counterpart of either of these, in an amount effective to suppress the expression of functional gene product of MSX1 and/or HES1, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a [neural progenitor,]neuronal[, or glial cell]; and

(d) growing the transdifferentiated cell in a medium comprising a retinoid compound and a signal molecule selected from the group consisting of brain-derived neurotrophic factor (BDNF), platelet-derived growth factor (PDGF), nerve growth factor (NGF), neurotrophin (NT)-3, neurotrophin (NT)-4;

wherein the physiological and/or immunological feature comprises expression of a neuronal cell marker selected from the group consisting of neurofilament M, neural-specific β-tubulin, neural-specific enolase, and microtubule associated protein 2, or a combination of any of these; and

wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length.

50. (Reiterated) The method of Claim 49, wherein the subject is a human.

51. (Reiterated) The method of Claim 49, wherein the epidermal basal cell(s) is derived from a skin biopsy.

52. (Reiterated) The method of Claim 49, wherein culturing the proliferating epidermal basal cell population further comprises separating keratinized epidermal cells from the epidermal basal cells in a calcium-free medium.

53. (Reiterated) The method of Claim 49, wherein the amount of the antagonist of bone morphogenetic protein is about 10^{-6} to 10^{-4} M.

54. (Reiterated) The method of Claim 53, wherein the amount of the antagonist of bone morphogenetic protein is about 5×10^{-6} to 5×10^{-5} M.

55. (Reiterated) The method of Claim 49, wherein the antagonist of bone morphogenetic protein (BMP) is fetuin, noggin, chordin, gremlin, or follistatin.

56. (Reiterated) The method of Claim 55, wherein the fetuin is mammalian or avian fetuin.

57. (Reiterated) The method of Claim 56, wherein the mammalian fetuin is human, bovine, porcine, ovine, or equine fetuin.

58. (Reiterated) The method of Claim 49, wherein the antisense oligonucleotide(s) is modified with one or more thio groups.

59. (Reiterated) The method of Claim 49, wherein the amount of the antisense oligonucleotide is about 5×10^{-6} M to about 10^{-5} M.

60. (Reiterated) The method of Claim 49, wherein the retinoid compound is all-trans retinoic acid or Vitamin A.

61. (Reiterated) A transdifferentiated cell of epidermal origin having one or more morphological, physiological and/or immunological feature(s) of a neuronal cell produced by the method of Claim 49, wherein the physiological and/or immunological feature comprises expression of a marker selected from the group consisting of neurofilament M, neural-specific β-tubulin, neural-specific enolase, and microtubule associated protein 2, or a combination of any of these; and wherein the morphological feature comprises one or more morphological neurite-like process(es) at least about 50 micrometers in length.

62. (Reiterated) The transdifferentiated cell of Claim 61, wherein the cell further exhibits a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

63. (Reiterated) The transdifferentiated cell of Claim 61, wherein the cell is a GABAergic cell.

64. (Reiterated) The transdifferentiated cell of Claim 61, wherein the cell is a dopaminergic cell.

65. (Reiterated) The transdifferentiated cell of Claim 61, wherein the cell is of human origin.

66. (Reiterated) A cell culture derived from the transdifferentiated cell of Claim 61, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a neuronal cell.